

## Editorial

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# The molecular basis of retinoids' use in breast cancer chemoprevention

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Whereas encouraging, interpretations of available data regarding retinoids' effectiveness in breast cancer chemoprevention, e.g. [5,7] fail to address pivotal molecular aspects concerning their employment in clinical trials.

The rationale for using retinoids in chemoprevention is primarily based on their ability to coordinately regulate differentiation, proliferation and apoptosis. The discovery of their receptors and cognate up- and downstream signaling cascades has emerged a great progress in the understanding of their molecular actions. Moreover, it has been recently suggested that the cross-talk between retinoid receptors and other signal transduction pathways might represent a "switch on/off" function model that is deregulated from the very early steps of carcinogenesis [3].

Retinoids, through retinoid acid receptors (RARs), mainly modulate proliferation/differentiation axes. In addition to their positive effects, particularly those correlated with differentiation, RARs also function as negative-acting transcription factors. One of the well-known transcriptional repressive effects of RARs is their inhibition of activator protein-1 (AP-1) activity. With regard to breast carcinogenesis, there is evidence that retinoids suppress estradiol-mediated proliferation and transcriptional activity and can antagonize the proliferative effects of AP-1. Crucial genetic/epigenetic events early in carcinogenesis, such as over-expression of epidermal growth factor receptor (EGFR) family proteins and gradual down-regulation of RAR $\beta$  ex-

pression, seem to favor AP-1 potentiation and, in turn, cyclin D1 over-expression that has been directly correlated with unopposed cellular proliferation [2]. Retinoids have also been shown to exert apoptotic effects during carcinogenesis. It has been postulated that a unique feature of fenretinide is its ability to inhibit cell growth through the induction of apoptosis rather than differentiation, although the exact molecular mechanism is not fully elucidated [8]. Notably, it has been demonstrated that the expression of HER-2/*neu* reduces the ability of fenretinide to trigger apoptosis in breast cancer cells, possibly via AP-1-mediated cyclooxygenase-2 (COX-2) induction [6].

If we combine the available clinical and molecular data, some important issues arise. First, it might be difficult to achieve a positive clinical result if only one axis of RARs action is targeted. For example, fenretinide particularly affects the apoptosis axis. Given the fact that proliferation and apoptosis are related to each other through molecular cross-talk, either targeting might produce a suboptimal clinical effect. Second, identifying molecules that mediate both RARs effects might be a rational approach. An appealing candidate is AP-1 as its signaling cascade and its co-factor network comprise a crucial molecular circuitry participating both in proliferation- and apoptosis-mediated effects [1]. Third, epigenetics represents a major mechanism of gene silencing in breast carcinogenesis. Thus, it should be possible to employ epigenetic-targeting agents in the treatment of retinoid-resistant breast tumors [4].

In conclusion, we think that the clinical effects of the currently used retinoids in breast cancer chemopre-

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vention trials should be interpreted as suboptimal, but also as an opportunity to integrate clinical and basic research data towards a rational use of the currently available nuclear receptor-targeted approaches and/or for the design of new potent and selective synthetic retinoids.

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